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MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/049,727 | GAWAD ET AL. | |
| | Examiner | Art Unit | |
| | Christine Foster | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2-13 and 16-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-13 and 16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Amendment*

1. Applicant's amendment, filed 2/26/2007, is acknowledged and has been entered. Claims 1 and 25-33 were canceled. Claims 2-13 were amended. Claims 2-13 and 16-24 are currently pending and under examination.

### *Objections/Rejections Withdrawn*

2. The objections to the specification and claims set forth in the previous Office action have been obviated by the amendments.

3. The rejections of claims 1-13 and 16-24 under 35 USC 112, 1st paragraph as containing new matter have been withdrawn in response to the amendments removing references to "platelet releasates", "platelet plasma" or "combinations" of fluids from the claims.

4. The rejection of claim 1 under 35 USC 102(b) as being anticipated by Sieffert et al. is withdrawn in light of the claim's cancellation.

### *Claim Rejections - 35 USC § 112*

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 2-13 and 16-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Independent claims 2-13 recite the step of "determining the amount of active PAI-1...by correlating the amount of active PAI-1 to the amount to the amount of active PAI-1/multimeric vitronectin complex in the sample". The claim is indefinite because the recited step states that that the amount of active PAI-1 is being used in order to determine itself, which is illogical. How can an unknown parameter be determined by correlating or comparing that unknown parameter to a second parameter, if the unknown parameter is not known? If the step of correlating is what allows the amount of active PAI-1 to be determined, it is unclear how the amount of active PAI-1 could be compared or correlated in this correlation step if it has not yet been determined. In addition, it is unclear how the two amounts are correlated in order to determine the amount of active PAI-1 in the biological fluid sample. Is the amount of the active PAI-1 being equated to the amount of complex measured? Are the two inversely related? The claim is ambiguous as to how the amount of active PAI-1 is being determined based on the process steps recited in the method, which refer only to measurement of the complex.

### *Claim Rejections - 35 USC § 103*

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 2-11 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamsten (*The New England Journal of Medicine* **10** (1995), 677-678) in view of Preissner et al. (*Blood* **74**:1989-1996 (1999), of record), Declerck et al. (*Journal of Biological Chemistry* **263** (1988), 15454-15461, of record), Wiman et al. ("Plasminogen activator inhibitor 1 (PAI) is bound to vitronectin in plasma" *FEBS Letters* 242 (1988), 125-128), and Harlow et al. (Antibodies: A Laboratory Manual (1988), Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, pages 555-559, 561-562, 278-581, 583, 591-592, and 605, of record).

Hamsten teaches a method of measuring the activity of PAI-1 in subjects who survived a first myocardial infarction in which high plasma PAI-1 activity independently predicted reinfarction within three years of the primary infarction (see the paragraph bridging p. 1-2). The reference teaches that there is a cause-and-effect relation between elevated plasma PAI-1 activity and myocardial infarction, establishing that at the time of the invention, measurement of PAI-1 activity was known in the art to be used for predicting myocardial reinfarction.

The teachings of Hamsten differ from the claimed invention in that Hamsten does not specifically teach measuring plasma PAI-1 activity by measuring active PAI-1 *in complex with multimeric vitronectin.*

Preissner et al. teach a method of measuring the amount of PAI-1 in complex with vitronectin in biological fluid samples including platelet releasates, platelet lysates, and other

biological fluids (see the entire document, in particular the abstract; p. 1990, left column, "Platelet preparation and aggregation", "Preparation of platelet releasate" and "Assay Methods"; p. 1992-1993, "Complex formation between vitronectin and plasminogen activator inhibitor-1 in platelet release"; and Figure 6).

Although Preissner et al. fail to specifically disclose that the PAI-1/vitronectin complex measured is a complex of **active** PAI-1 with vitronectin, the instant specification discloses at p. 2, lines 15-20 that it is **active** PAI-1 that is bound to vitronectin. Consequently, the PAI-1 that is in complex with vitronectin is necessarily active PAI-1 (see also the previous Office action at p. 9 and the Office action mailed 1/12/2006 at page 9). It was also known in the prior art that complexed PAI-1 is **active** PAI-1, as Wiman et al. teaches that functionally active PAI-1 in plasma is complexed with a binding protein identified as vitronectin (see the abstract and p. 125, left column). In contrast, functionally inactive or "latent" PAI-1 has a lower apparent molecular weight of 50 kDa, which corresponds with the molecular weight predicted from the primary structure of PAI-1, indicating that inactive PAI-1 exists in free or uncomplexed form. Thus, it was known in the art at the time of the invention that PAI-1 in complex with vitronectin is active PAI-1.

With regard to the particular mode of measuring the PAI-1-vitronectin complex as recited in claims 2, 4, and 23, Preissner et al. teach contacting the biological fluid sample with a first antibody that binds selectively to PAI-1 (PAI-1 monoclonal antibodies) and a labeled second antibody that binds selectively to vitronectin (polyclonal anti-vitronectin IgG that is labeled with biotin). Preissner et al. further teach determining the second antibody bound to the complex by

incubating the labeled (biotinylated) second antibody with peroxidase-conjugated avidin (see p. 1990, right column, the third full paragraph in particular). See also Figure 6.

The mode of measurement of PAI-1/vitronectin complex in Preissner et al. differs from the claimed invention in that Preissner fail to specifically teach detecting PAI-1 in complex with the **multimeric** form of vitronectin. In the reference, a sandwich ELISA assay was used to detect the PAI-1-vitronectin complex. However, because the ELISA used polyclonal anti-vitronectin antibodies, which would not distinguish between the multimeric and monomeric forms of vitronectin, Preissner et al. do not specifically teach detecting PAI-1 in complex with the **multimeric** form of vitronectin.

The prior art at the time of the invention recognized, however, that vitronectin exists in multimeric as well as monomeric forms. In fact, Preissner et al. teach multimeric (dimeric) and monomeric forms of vitronectin (p. 1991, right column). Importantly, Preissner et al. also teach that the different forms of vitronectin are immunologically distinguishable, in that the monoclonal anti-vitronectin antibody VN-P1C5 bound selectively to the non-reduced, multimeric vitronectin but not to the reduced, monomeric protein (p. 1991, right column, the first paragraph). See also the data Figure 3, where the samples were analyzed by Western blot analysis under both non-reducing conditions (allowing the multimeric form to be visualized) and under reducing conditions (where the multimeric form is reduced to monomer). Compare Figure 3B, lanes 2 and 5, under non-reduced and reduced conditions.

As noted above, Wiman et al. teach that functionally active PAI-1 in plasma is complexed with a binding protein identified as vitronectin (see the abstract and p. 125, left column). In contrast, functionally inactive or "latent" PAI-1 has a lower apparent molecular

weight of 50 kDa, which corresponds with the molecular weight predicted from the primary structure of PAI-1, indicating that inactive PAI-1 exists in free or uncomplexed form. However, it is noted that Wiman et al. do not address the issue of whether vitronectin bound to PAI-1 is monomeric or multimeric. Nonetheless, the reference is pertinent to the instant claims because it establishes that it is the functionally active, rather than the latent form, of PAI-1 that exists in complex with vitronectin.

DeClerck et al. teach that PAI-1 exists in complex with vitronectin (see the entire document, in particular the abstract), in accordance with the teachings of Wiman et al. DeClerck et al. further characterized the PAI-1-vitronectin complex and demonstrated that the complex comprises the **multimeric** form of vitronectin (see the title; p. 15454, right column; p. 15459-15461, especially at p. 15459, the right column; and the paragraph bridging p. 15460-15461). As such, DeClerck et al. teach that it is specifically the multimeric form of vitronectin that binds to PAI-1.

Harlow et al. teach that immunoassay methods can be powerful, quick and easy methods for detection and quantification of antigens (p. 555). Specifically, Harlow et al. teach that two-antibody sandwich assays, which is the assay format used by Preissner et al. above, are especially useful (p. 579).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to measure the amount of active PAI-1/multimeric vitronectin complex in plasma as a marker of disease in order to predict myocardial reinfarction. Motivation to do so comes from the teachings of Hamsten that levels of active PAI-1 in plasma correlate with disease, and from the teachings of DeClerck et al. and Wiman et al, which establish that the functionally **active**

population of PAI-1 that is a disease marker exists in complex with the **multimeric** form of vitronectin, while inactive PAI-1 is not found in this complex. Since the art recognized active PAI-1 in plasma as a marker of disease, and further recognized that the active population of this marker exists in complex with multimeric vitronectin, to detect this complex as a marker of disease would have been obvious. In addition, one would be motivated to measure the amount of the PAI-1/vitronectin complex by ELISA as taught by Preissner et al. in light of Harlow, which teaches the power and ease of such immunoassay methods. Based on the teachings of Hamsten that levels of active PAI-1 in plasma correlate with disease, it would have been obvious to employ plasma as a sample source. Furthermore, although Preissner et al. exemplify platelet releasates and lysates, one skilled in the art would have a reasonable expectation of success in using an ELISA method rather than the activity assay mentioned in Hamsten et al. since Preissner teach that their assay methods can be used with other biological fluids (see especially page 1990, left column, the last paragraph).

One would have a reasonable expectation of success in measuring multimeric, rather than all forms of vitronectin complexed with PAI-1 because Preissner et al. teach the monoclonal anti-Vn antibody VN-P1C5, which recognizes only dimeric (multimeric) but not monomeric or reduced vitronectin (see p. 1991, right column, the first paragraph; and Figure 3 and legend, especially at Figure 3, lanes 2 and 5).

With respect to claims 3, 5, 9, and 11, the ELISA assay taught in Preissner et al. differs from these dependent claims in that Preissner et al. teach a first antibody that selectively binds to PAI-1 and a labeled second antibody that selectively binds to vitronectin, which is the converse.

However, Harlow et al. teach that in methods of detecting and quantitating antigens using a two-antibody sandwich assay, the choice of which antibody to label is determined empirically, and that both combinations of solid-phase and labeled antibody should be tried to determine which is best (p. 580, item 1).

Therefore, it would have been obvious to one of ordinary skill in the art to employ the anti-vitronectin antibody as the solid phase antibody and the anti-PAI-1 antibody as the labeled antibody in the method of Preissner et al. because Harlow et al. teach that both combinations should be tried in order to determine which is best in a two-antibody sandwich assay method, such as that of Preissner et al.

Although Preissner et al. fail to explicitly teach that the PAI-1/multimeric vitronectin/first antibody/second antibody complex was separated from the sample prior to determining the second antibody, as in claim 4, it would be immediately apparent to one skilled in the art that the 96-well microwell plate was washed following addition of the second antibody in accordance with standard ELISA assay techniques. This is evidenced by Harlow et al. at p. 579, the second paragraph.

With regard to claims 6 and 8, Preissner et al. teach that the sample is contacted simultaneously with both the first and second antibodies in that both antibodies are bound to the complex at the time of detection.

With regard to claims 7 and 24, the PAI-1 monoclonal antibodies were immobilized (coated) onto a solid support (96-multiwell plates). These plates would be considered to be an ELISA plate since they are plates upon which the ELISA assay is carried out.

With regard to claim 10, Preissner also teach a method wherein the second antibody is non-biotinylated polyclonal anti-vitronectin IgG, and wherein the 96-microwell plate is instead contacted with peroxidase-conjugated swine (antirabbit) IgG that binds to the second antibody; in this embodiment, the peroxidase-labeled third antibody is then determined (see p. 1990, right column, the third full paragraph in particular).

11. Claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamsten in view of Preissner et al., Declerck et al., Wiman et al., and Harlow et al. as applied to claims 2-11 and 23-24 above, and further in view of Forrest et al. (US 4,659,678).

It is acknowledged that claims 12-13 have been currently amended in the form of independent claims. However, it is noted that the claims are substantially similar to claims 2-11 and 23-24 with the exception that claims 12-13 recite that the first antibody *is attached to one member of a capture pair* and that the sample-first antibody-second antibody mixture is contacted with a solid support *on which is immobilized the other member of the capture pair.*

Because of this similarity, the detailed analysis of the Hamsten, Preissner et al., Declerck et al., Wiman et al., and Harlow et al. references provided above for claims 2-11 and 23-24 is equally applicable to the instant claims; Applicant is therefore referred to the detailed discussion of the references set forth above in regards to claims 2-11 and 23-24.

Briefly, based on the teachings of Hamsten, Preissner et al., Declerck et al., Wiman et al., and Harlow et al. it would have been obvious to one of ordinary skill in the art at the time of the invention to measure the amount of active PAI-1/multimeric vitronectin complex in plasma as a marker of disease in order to predict myocardial reinfarction. Motivation to do so comes from the

teachings of Hamsten that levels of active PAI-1 in plasma correlate with disease, and from the teachings of DeClerck et al. and Wiman et al, which establish that the functionally **active** population of PAI-1 that is a disease marker exists in complex with the **multimeric** form of vitronectin, while inactive PAI-1 is not found in this complex. Since the art recognized active PAI-1 in plasma as a marker of disease, and further recognized that the active population of this marker exists in complex with multimeric vitronectin, to detect this complex as a marker of disease would have been obvious. In addition, one would be motivated to measure the amount of the PAI-1/vitronectin complex by ELISA as taught by Preissner et al. in light of Harlow, which teaches the power and ease of such immunoassay methods.

The method of Hamsten, Preissner et al., Declerck et al., Wiman et al., and Harlow et al. differs from the invention claimed in claims 12-13 in that the references fail to specifically teach that the first antibody *is attached to one member of a capture pair* and in which the sample-first antibody-second antibody mixture is contacted with a solid support *on which is immobilized the other member of the capture pair.*

Forrest et al. teaches methods of immobilizing antibodies to solid phase supports for use in immunoassays. In particular, Forrest et al. teach sandwich-type immunoassays using two antibody reagents, in which one of the antibodies is labeled and in which the other is non-covalently bound to a solid phase support (column 2, line 44 to column 3, line 68). The solid phase-bound antibody may be bound by use of a specific binding protein such as avidin or biotin, which constitute a very rapid, high affinity binding system, or by use of a third antibody directed against a reagent such as FITC that is attached to the antigen antibody; the third antibody is first linked to the solid support and then used to capture the antigen antibody (column 2, lines 52-58;

column 4, line 55 to column 5, line 20). Forrest et al. further teach that the antigen is contacted with both antibodies prior to the addition of the solid phase component (see in particular column 5, lines 28-34 and column 8, lines 43-55).

Therefore, it would have been obvious to label the first antibody with avidin or biotin for immobilizing to the solid support because Forrest et al. teach that such specific binding proteins constitute a very rapid, high affinity binding system for immobilizing antibodies to solid supports. It would have been further obvious to contact the sample with the first and second antibodies and then to contact the mixture with the solid support with bound avidin or biotin because Forrest et al. teach that this is preferable. One would have a reasonable expectation of success because Forrest et al. is also drawn to sandwich-type solid phase immunoassays employing two antibodies directed to distinct epitopes of an antigen.

12. Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamsten in view of Preissner et al., Declerck et al., Wiman et al., and Harlow et al. as applied to claim 3 above, and further in view of Ehrlich et al. (US 5,665,548).

Hamsten in view of Preissner et al., Declerck et al., Wiman et al., and Harlow et al. are as discussed above. The references teach an assay format in which the second antibody is indirectly labeled with peroxidase (via biotin-avidin interaction), but fail to specifically teach that the second antibody is *directly* labeled.

Ehrlich et al. teach that in sandwich immunoassays, it is well known in the art that the labeled antibody may be labeled with a directly or indirectly detectable label, and that either is suitable so long as it allows for the detection of the antibody when bound to a solid support

(column 27, line 39 to column 28, line 10). Ehrlich et al. teach that a preferred direct label is an enzyme, conjugated to the antibody, which produces a color reaction, such as horseradish peroxidase (column 27, lines 47-50).

Therefore, it would have been obvious to one of ordinary skill in the art to directly rather than indirectly label the second antibody with the peroxidase label because Ehrlich et al. teach that indirect and direct labels are both suitable for sandwich immunoassays, which is the assay format used by Preissner et al. and Harlow et al.

13. Claims 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamsten in view of Preissner et al., Declerck et al., Wiman et al., and Harlow et al. as applied to claim 3 above, and further in view of Valenzuela et al. (US 6.428,792 B1).

The references are as discussed above, which teach an assay format in which the second antibody is labeled with biotin, but fail to specifically teach that the label is a fluorophore or a luminescent material.

Valenzuela et al. teach that antibody labels known in the art also include fluorophores such as rhodamine and luminescent materials such as acridinium ester compounds (column 3, line 58 to column 4, line 7).

Therefore, it would have been obvious to one of ordinary skill in the art to employ a fluorophore such as rhodamine or a luminescent material such as an acridinium ester as taught by because Valenzuela et al. teach that such compounds are commonly known antibody labels for use in immunoassays for detection of immunocomplexes.

***Response to Arguments***

14. Applicant's arguments filed 2/26/2007 have been fully considered.

15. With respect to the rejection of claim 1 under 35 US 112, 2nd paragraph (now applied above to independent claims 2-13), Applicant argues that the term "said amount" has been removed (Reply, page 13). However, the lack of antecedent basis was only one aspect of the rejection, and therefore, Applicant's arguments and amendments do not fully address the rejection. The independent claims recite:

> [D]etermining the amount of active PAI-1...by correlating the amount of active PAI-1...to the amount of active PAI-1/multimeric vitronectin complex

In essence, the step states that the value of an unknown parameter (the amount active PAI-1) is determined by correlating or comparing that same unknown parameter to a second, known parameter (the amount of active PAI-1/multimeric vitronectin complex). The claim is indefinite because it is unclear how the two parameters may be correlated or compared in order to determine one of the parameters; this is circular logic. If the amount of active PAI-1 is ***unknown***, how can it be correlated or compared with the amount of complex in order to determine itself? It is maintained for reasons of record that the claim is indefinite.

16. With respect to the rejections of claims 1-11 and 23-24 under 35 USC 103(a) as being unpatentable over Hamsten in view of Preissner et al., Declerck et al., Wiman et al., and Harlow et al., Applicant's arguments (see Reply, page 14-19) have been fully considered but are not persuasive.

17. Applicant argues that DeClerck et al. teaches away from the claimed invention in that it teaches that PAI-1 binds to both monomeric and oligomeric vitronectin (Reply, page 17). The Examiner disagrees that the noted passage teaches rises to the level of a teaching away. The

reference teaches that the vitronectin that existed in complex with PAI-1 was "mainly" the oligomeric form, although "some" of the monomeric form could also be identified. The authors conclude that "**PAI-1 binds to both monomeric and oligomeric S protein, but preferentially to the multimeric form**" (p. 15460, left column). The fact that Declerck disclose that some PAI-1 was also found complexed with monomeric vitronectin does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed. Therefore, Applicant's arguments are not persuasive because the disclosure that PAI-1 preferentially binds to multimeric vitronectin cannot be characterized as a "teaching away" since the reference as a whole teaches PAI-1 predominantly forms complexes with multimeric vitronectin over the monomeric form.

18. Applicant further argues in regard to the characterization that Preissner et al. inherently teaches determination of active PAI-1 since PAI-1 bound to vitronectin is inherently active, that inherency cannot be used to support an obviousness rejection (see pages 17-18). Applicant's arguments are not persuasive because as noted in the rejection, it was in fact known in the prior art that PAI-1 bound to vitronectin is active PAI-1, as taught for example in Wiman et al. (see the previous Office action at page 10, the first full paragraph). Thus, the rejection is not based solely on the fact that Preissner et al. necessarily determined active PAI-1, since in this case the record reflects that it was known in the art at the time of the invention that it is the active form of PAI-1 that exists in complex with vitronectin.

19. Applicant further argues that none of the cited references teach that the amount of active PAI-1 can be determined by measuring the amount of PAI-1/multimeric vitronectin complex in a sample, or that active PAI-1 is bound to multimeric vitronectin (Reply, page 17, the first full

paragraph; and page 18, the first full paragraph). Such arguments are not persuasive since they amount to a piecemeal analysis of the references; however, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Wiman et al. teach that functionally active PAI-1 is complexed with vitronectin. Although Wiman et al. do not specifically address whether this complex involves monomeric or multimeric vitronectin, such a teaching is found in Declerck et al., as discussed above. Taken together, the references establish that it was known in the art at the time of the invention that active PAI-1 is bound to multimeric vitronectin.

20. Applicant further argues that because platelet releasates and platelet lysates are not taught or supported by the present specification, that they are not enough to maintain an obviousness rejection (page 18). The argument is not persuasive because it does not logically follow that matter not originally disclosed in a patent application is necessarily non-obvious over the prior art. Whether subject matter is adequately described by the original disclosure or alternatively represents new matter is a separate legal determination (for compliance with 35 USC 112, 1st paragraph) than the determination of whether the claimed invention as a whole is obvious over the prior art under 35 USC 103.

The courts have also recognized this distinction; for example in Lockwood v. American Airlines, Inc., later-claimed subject matter was found to be insufficient to meet the written description requirement despite being obvious over a disclosure in a parent application. See Lockwood v. American Airlines, Inc., 107 F.3d 1565 (Fed. Cir. 1997).

21. Applicant further argues that the invention as a whole must be found in the references cited, and that the claimed invention is an assay for biological fluids selected from whole blood, plasma, and serum, and are no longer claiming platelet releasates and platelet lysates as taught in Preissner. However, as noted above, Hamsten et al. teach that PAI-1 activity in *plasma* is a predictor of myocardial reinfarction. Based on such teachings, it would have been obvious to employ plasma as a sample source since plasma PAI-1 was recognized in the prior art as a biomarker of disease. Furthermore, although Preissner et al. exemplify platelet releasates and lysates in detecting PAI-1 in complex with vitronectin, one skilled in the art would have a reasonable expectation of success in using ELISA methods such as those in Preissner et al. given that the reference teaches that the assay methods can be used with other biological fluids (see especially page 1990, left column, the last paragraph).

22. Applicant further argues that the Office action states that the VN-P1C5 antibody of Preissner et al. binds selectively to multimeric vitronectin, and that such a statement is contradictory to the statement in the Office action that Preissner et al. does not specifically teach PAI-1 in complex with multimeric vitronectin (Reply, page 18). The examiner notes that the statements are not contradictory: while Preissner et al. does not specifically direct the skilled artisan to detect PAI-1 in complex with *multimeric* vitronectin, the VN-P1C5 antibody taught in the reference is in fact an antibody that does selectively bind to the multimeric (dimeric) form. Specifically, as noted in the rejection, Preissner et al. teach that the VN-P1C5 antibody recognized dimeric vitromectin, but did not show any reaction with the reduced (monomeric) sample (page 1991, right column, first paragraph).

Applicant further argues that the complex in the non-reduced gels in Figure 3B would of necessity be monomeric rather than vitronectin (Reply, page 18, the last paragraph). Such an interpretation is contrary to the evidence of record. Preissner et al. specifically teach that the non-reduced gels feature **dimeric** vitronectin, as noted at page 1991, right column, the first paragraph. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). Absent any evidence of record that would support Applicant's interpretation, rather than that of the study's authors, it is maintained that Preissner et al. clearly teach that the VN-P1C5 antibody of Preissner et al. binds selectively to multimeric (dimeric) vitronectin. Consequently, Applicant's arguments that Preissner et al. teaches away from the claimed invention are not persuasive because they are based on an interpretation of the reference that is not supported by any evidence of record.

23. Applicant further argues that the claimed invention is distinguished over the prior art in that the prior art methods would require an excess of antibody (Reply, page 19, the second full paragraph). However, it is noted that the features upon which applicant points are not recited in the rejected claim(s), which do not recite any limitations as to the amount of antibody to be employed. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

24. With respect to the rejections of claims 12-13 under 35 USC 103(a) as being unpatentable over Hamstem in view of Preissner et al., Declerck et al., Wiman et al., and Harlow et al., and further in view of Forrest et al., Applicant has not separately argued the additional limitations

that pertain to these claims but refers to the arguments made with respect to Hamsten, Preissner et al., Declerck et al., Wiman et al., and Harlow et al. that have been addressed above.

25. With respect to the rejections of claims 16-18 under 35 U.S.C. 103(a) as being unpatentable over Hamsten in view of Preissner et al., Declerck et al., Wiman et al., and Harlow et al., and further in view of Ehrlich et al., Applicant has not separately argued the limitations of the dependent claims.

26. Claims 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hamsten in view of Preissner et al., Declerck et al., Wiman et al., and Harlow et al., and further in view of Valenzuela et al., Applicant has not separately argued the limitations of the dependent claims.

***Conclusion***

27. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The

examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CFoster

Christine Foster, Ph.D.
Patent Examiner
Art Unit 1641

LONG V. LE 05/13/07
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600